AMENDMENTS TO THE SPECIFICATION

Please replace the last paragraph on page 25 and continuing on to page 26 of the specification with the following rewritten paragraph:

Previous studies utilizing the rP-8/4x ribozyme (Testa, S. M., Gryaznov, S. M. & Turner, D. H. (1998) *Biochemistry* **37**, 9379-9385) show that the 5' exon mimic r(AUGACU) binds to the rP-8/4x ribozyme (K_d = 5.2 nM at 37 °C) three orders of magnitude more tightly than the 3' exon mimic r(GUGCUCU) ~~(SEQ ID NO. 7)~~ ($K_d \approx$ 20 μM at 37 °C). Interestingly, maximum TES product formation occurs with as little as 20 nM ribozyme (at 44 °C), indicating that for final product formation the 5' and 3' exon intermediates produced during the 5' cleavage step might not dissociate and then rebind the ribozyme before the exon ligation step. To test for 5' exon dissociation and rebinding between the two steps, TES reactions were conducted with 166 nM rP-8/4x, 1.33 nM non-radiolableled 36-mer, and 1.33 nM radiolabeled 5' exon, r(AUGACU) ~~(SEQ ID NO. 8)~~. In this case, if the 5' exon intermediate dissociates from the ribozyme, the radiolabeled 5' exon is just as likely to then bind the ribozyme and form the 16-mer product as the non-radiolabeled 5' exon intermediate. As seen in Figure 5, no radiolabeled TES products are observed, indicating the 5' exon intermediate does not dissociate from the ribozyme between the two steps (for those 5' exon intermediates that undergo the complete reaction).

Please replace the last paragraph on page 26 and continuing on to page 27 of the specification with the following rewritten paragraph:

Likewise, to test for 3' exon intermediate dissociation and rebinding between the two reaction steps, TES reactions were conducted with 166 nM rP-8/4x, 1.33 nM radiolabeled 36-mer, and a 50 (66.5 nM) or 500 (665 nM) fold excess of a non-radiolabeled 3' exon mimic competitor, r(GUGCUCU) ~~(SEQ ID NO. 7)~~, which would form a 10-mer competition product. At equal molar concentrations if the 3' exon intermediate dissociates from the ribozyme, the 7-

mer competitor is 2.5 times more likely to bind the ribozyme and be a substrate in the second reaction step than the 30-mer 3' exon intermediate (data not shown). The results (Figure 5) show that a 500-fold excess of cold competitor over substrate does not significantly reduce the amount of 16-mer product formed (19.4% ± 2.3% versus 22.8% ± 3%, respectively). The small amount of 10-mer product that is observed at 500-fold excess competitor over substrate (but not 50-fold excess) is not actually competing with the TES reaction. In these cases, the ribozymes that have bound radiolabeled 5' exon regions, and for which the 3' exon region has dissociated, are binding and reacting with a small amount of the huge excess of 3' exon competitor. Therefore, the vast majority of substrates that undergo the complete TES reaction do not have 3' exon intermediate dissociation and rebinding occurring between the two steps of the reaction. Apparently, substrates that undergo only the first reaction step do so because of nearly irreversible 5' or 3' exon intermediate dissociation. It follows that since intermediates to the complete TES reaction do not dissociate from the ribozyme, the TES reaction is intramolecular with regard to substrate.

Please insert after page 30, but before the claims, the attached paper Sequence Listing in the specification.

Attachments: Sequence Listing (paper copy)
Sequence Listing (computer readable disk copy)

AMENDMENTS TO THE DRAWINGS

The attached replacement formal drawing sheets for Figures 1-7 include Figures 1A, 1B, 2A, 2B(i), 2B(ii), 2B(iii), 3A, 3B, 3C, 4, 5, 6A, 6B, 7A, 7B, 7C(i) and 7C(ii), and respectively replace the original sheets including Figures 1, 2A, 2B(i)-(iii), 3A, 3B, 3C, 4, 5, 6A, 6B and Figure 7 inadvertently labeled as Figure 6 again, but consisting of three figures A, B and C. The replacement formal drawing sheets for Figures 1-7 correct the errors in the figure labeling.

Attachment: Replacement Formal Drawing Sheets for Figures 1A, 1B, 2A, 2B(i), 2B(ii), 2B(iii), 3A, 3B, 3C, 4, 5, 6A, 6B, 7A, 7B, 7C(i) and 7C(ii).